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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
QAZI, SABIHA NAIM	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 08/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/641,327	AGOSTON ET AL.	
	Examiner	Art Unit	
	Sabiha Qazi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *13-16,18 and 39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *39* is/are rejected.

7)☐ Claim(s) *13-16, 18 and 39* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Final Rejection

Acknowledgement is made of the response filed on . Amendments are entered. Claims 13-17 and 39 are pending. No claim is allowed.

Instant claims are drawn to method of inhibiting angiogenesis by 2-methoxy, 16-substitued estradiols.

Prior art of record teaches method of treatment of angiogenesis, for example 2-methoxy estradiol, 2-ethoxy estradiol, 2-alkoxyestradiol derivatives, esterone, 2-hydroxyalkylestradiols, All the compounds are estradiol derivatives known to treat angiogenesis or cancer. Prior does not teach 16-substituted 2-alkoxy compounds as presently claimed in claims 13-16 and 18.

Response to Arguments

- Applicants submit that "in the art of estradiols is highly unpredictable".
- Examiner notes, that one example disclosed contain 16-methyl-substituted estradiol. Considering the unpredictability the claimed method of treating angiogenesis having various substituents at 16-position would not be obvious to one skilled in the art. Applicant is requested to explain how angiogenesis can be treated as claimed by the teachings in the disclosure. Some disclosure is noted at page 33 and 34 of the specification.
- A typing error has been noted in claim 39, "compound" should be "a group" or any other appropriate language.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 39 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The proviso inserted by amendments is considered "new matter" because there is no support in the disclosure. Applicant is requested to show if there is any support for this negative proviso.

MPEP 2173.05(i) states:

"Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See In re Johnson, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining."). See also Ex parte Grasselli, 231 USPQ 393 (Bd. App. 1983), aff'd mem., 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. **Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement.**"

The claims are rejected under 35 U.S.C. 112, first paragraph, under instruction from MPEP 2173.05(i), because they contain a negative limitation which does not have basis in the original disclosure.

In *In re Johnson*, the court noted that any negative limitation or exclusionary proviso ***must have basis in the original disclosure.*** ***Only*** if alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. The negative

limitation/exclusionary proviso does not have basis in the original disclosure, and the alternative elements were not positively recited in the specification, so the Appellants' argument is not relevant to the current issues.

In *Purdue Pharma LP v Faulding, Inc., 230 F.3d 1320, 1326, 56 USPQ2d 1481, 1486 (Fed. Cir. 2000)*, the court noted that with respect to *In re Ruschig, 371 F.2d 990, 154 USPQ 118 (CCPA 1967)*, "Ruschig makes clear that one cannot disclose a forest in the original application, and then later pick out a tree of the forest and say "here is my invention". In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure."

Purdue is more relevant, because the Appellants disclosed a genus ("a forest") in the original application, then later picked out two specific compounds ("a tree of the forest"), and are now saying, "here is my invention". In order to satisfy the written description requirement, according to *Purdue*, the Appellants must disclose the specific compounds in the originally filed disclosure."

More from *Purdue*: The case of In re Ruschig, 379 F.2d 990, 154 USPQ 118 (CCPA 1967), is instructive here. In that case our predecessor court affirmed the holding of the Patent Office Board of Appeals that one of the claims, adopted for purposes of interference, was not supported by the disclosure. The claim at issue in that case was directed to a single compound. The applicants argued that, although the compound itself was not disclosed, one skilled in the art would find support for the claimed compound in the general disclosure of the genus of compounds to which the claimed compound belonged. The Ruschig court rejected that argument,

stating:

[i]t is an old custom in the woods to mark trails by making blaze marks on the trees. It is of no help in finding a trail or in finding one's way through the woods where the trails have disappeared-or have not yet been made, which is more like the case here-to be confronted simply by a large number of unmarked trees. We are looking for blaze marks which single out particular trees. We see none.

Id. at 994-95, 154 USPQ at 122. Although this case differs from Ruschig in that what was disclosed in Ruschig was a genus encompassing potentially half a million compounds, the rationale applies equally to this case, in which the disclosure of the '360 patent discloses a multitude of pharmacokinetic parameters, with no "blaze marks" directing the skilled artisan to the C_{max}/C_{24} ratio or what value that ratio should exceed. See id. at 994, 154 USPQ at 122 ("Specific claims to single compounds require reasonably specific supporting disclosure and while we agree with the appellants, as the board did, that naming is not essential, something more than the disclosure of a class of 1000, or 100, or even 48, compounds is required."). As Ruschig makes clear, one cannot disclose a forest in the original application, and then later pick a tree out of the forest and say "here is my invention." In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure. See id. at 994-95, 154 USPQ at 122; Fujikawa, 93 F.3d at 1570-71, 39 USPQ2d at 1905; Martin v. Mayer, 823 F.2d 500, 505, 3 USPQ2d 1333, 1337 (Fed. Cir. 1987) ("It is `not a question of whether one skilled in the art might be able to construct the patentee's device from the teachings of the disclosure . . . . Rather, it is a question whether the application necessarily

discloses that particular device.'") (quoting Jepson v. Coleman, 314 F.2d 533, 536, 136 USPQ 647, 649-50 (CCPA 1963)). Under that standard, we conclude that the district court did not commit clear error in finding that nothing in the '688 application "'necessarily' . . . described the later claimed subject matter" of the '360 patent. In re Daniels, 144 F.3d 1452, 1456, 46 USPQ2d 1788, 1790 (Fed. Cir. 1998).

Data in the specification

On page 33, Table 2 shows the test data for the compounds 2-methylhydroxy-E2, (2ME2 is known), and other compounds having 2-methoxy, 16-substitued compounds. Applicants filed on 10/7/2004 to correct a typing error have amended the substituent R in Table 2 on Page 33. Specification discloses 16-modified analogs presented in Table 2 have significantly less estrogenic activity (compared to estradiol). The most active compound in this series as disclosed is 16alpha methyl compound, which has a greater activity than 2-methoxy estradiol when no methyl is at 16-position. (See line 12-13 on page 33. However, the IC50 disclosed shows no actual number but <0.5. The IC50 of known methoxy estradiol is 0.5. It is unclear what is the actual difference. Is the difference is in the expected range?

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Entere Med, 2Me2-Non-confidential Overview, Angiogenesis Company, Updated 7/11/00 and Attala et al. (Biomedical and Biophysical Research Communication 228, 467-473 (1996). The references teach the method of inhibiting angiogenesis by 2-methoxy estradiol. See especially page 6 of the article from Angiogenesis Company.

The prior art of record is drawn to structurally similar compounds, which differ, from the compounds embraced by the instant claims in that they are homologues, i.e. H vs. Me or Et at 16-position. The skilled artisan would have been motivated to modify the teaching of the prior art to prepare homologues because it is recognized in the art that homologues are structurally

similar and would be expected to possess similar properties. *Ex parte Henze* (POBA 1948) 83 USPQ 167.

Compounds that differ only by the presence of an extra methyl group are homologues. Homologues are of such close structural similarity that the disclosure of a compound renders prima facie obvious its homologue.

The homologue is expected to be prepared by the same method and to have the same properties. This expectation is then deemed the motivation for preparing homologues. See *In re Wood* 199 USPQ 137; *In re Hoke* 195 USPQ 148; *In re Lohr* 137 USPQ 548; *In re Magerlein* 202 USPQ 473; *In re Wiechert* 152 USPQ 249; *Ex parte Henkel* 130 USPQ 474; *In re Fauque* 121 USPQ 425; *In re Druey* 138 USPQ 39.

In absence of any criticality and/or unexpected results instant invention is considered obvious over the prior art of record.

In the light of the forgoing discussion, the Examiner's ultimate legal conclusion is that the subject matter defined by the instant claims would have been obvious within the meaning of 35 U.S.C. 103(a).

Allowable Subject Matter

Claims 13-16 and 18 are objected for being dependent on a rejected claim but when written independently are allowable.

Prior art of record does not teach nor fairly suggests the steroids of formula in claim 1 when 16-position is substituted by Rh1 and Rh2 by n-Pr, I-Bu, CH2OH, n-Bu, Me, or (CH2) n N(Me)2 wherein n is from 1 to 6 and provided that Rh1 and Rh2 are not H.

Conclusion

3. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sabiha Qazi whose telephone number is (571) 272-0622. The examiner can normally be reached on any business day.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Thursday, August 05, 2005

SABIHA QAZI, PH.D
PRIMARY EXAMINER